Effects of Esophageal Acid Perfusion on Cough Responsiveness in Patients With Bronchial Asthma*

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Study objectives: The effect of gastroesophageal reflux (GER) on cough responsiveness in patients with bronchial asthma has yet to be studied in significant detail. The purpose of this study was to assess the effect of distal esophageal acid perfusion on cough responsiveness in patients with bronchial asthma.

Patients and interventions: In seven patients with mild persistent bronchial asthma (mean age, 57.7 ± 3.7 years; four women and three men), esophageal pH was monitored by a pH meter and cough responsiveness was evaluated by single-breath aerosol inhalation of capsaicin with increasing dosage from 0.30 to 9.84 nmol. Simultaneously, esophageal perfusion was performed through an esophageal tube filled with either saline solution or 0.1 N hydrochloric acid (HCl), the order of which was selected at random, in 1-week intervals. Results were expressed as the lowest concentration of capsaicin eliciting three coughs (PD₃). Spirometry was also performed during esophageal pH monitoring.

Results: A significant decrease in the geometric mean of log PD₃ was observed during distal esophageal HCl perfusion (0.45 ± 0.04 nmol) compared with that of the saline solution perfusion (0.04 ± 0.06 nmol) [p < 0.01]. However, no significant changes were observed either in FVC, FEV₁, or peak expiratory flow during the periods of the saline solution or HCl perfusion.

Conclusion: The present data demonstrate that an increase in cough responsiveness may be induced when HCl stimulates the distal portion of esophagus in patients with bronchial asthma, suggesting that the GER would be one of the important factors that influence asthmatic status.

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Key words: bronchial asthma; cough responsiveness; esophageal acid perfusion; gastroesophageal reflux

Abbreviations: GER = gastroesophageal reflux; LES = lower esophageal sphincter; PD₃ = concentration of capsaicin causing three or more coughs; PEF = peak expiratory flow

There is a potential association between asthma and gastroesophageal reflux (GER), with GER being a potential trigger in selected patients.¹–⁶ Chronic cough and asthma are two clinical problems caused or triggered by GER disease.⁵,⁷ Irwin et al⁷ indicated chronic persistent cough correlated with distal but not proximal acid reflux events usually showing evidence of distal esophagitis observed with endoscopy; they concluded that acid stimulated inflamed distal esophageal mucosal receptors, resulting in a reflex-mediated cough. However, the effect of GER on cough responsiveness in patients with bronchial asthma has not yet been adequately studied.⁸–¹³ The purpose of the present study was to determine whether distal esophageal acid perfusion itself could alter cough responsiveness in patients with bronchial asthma even if there was no evidence of esophagitis.

Materials and Methods

Patients

Seven patients with mild persistent bronchial asthma (four women and three men; mean ± SD age, 57.7 ± 3.7 years; range, 39 to 64 years) took part in the study. All patients satisfied the criteria for asthma published by the National Institutes of Health.¹⁴ We performed esophagogastroscopey on all patients in...
of hot pepper, was prepared by dissolving 3.0 mg of the substance
in 10 mL of 95% ethanol. The nebulizer was attached to the
Aerosol was delivered by a jet nebulizer attached to the
mouthpiece of the patients. The nebulizer was set to nebulize for 0.9 s at a pressure of 21
cm H 2 O. In the present study, we used PD 3 as the dose to express cough sensitivity of all subjects. The results were reproducible with capsaicin as two separate administration for the preliminary examination. If no cough was elicited by the highest tested dose, PD 3 was arbitrarily given the value 19.7 nmol (i.e., twice the highest tested dose).

Statistics

Two-way analysis of variance was used to compare the results of different continuous variables in the two perfusion periods. As a follow-up to the analysis of variance, the Tukey studentized range test was used to compare the different parameters between the two periods. The PD 3 data were log transformed. Data are expressed as mean ± SD. The accepted statistical significance was p < 0.05.

Results

The patients’ characteristics are presented in Table 1. All patients had mild asthmatic symptoms without symptoms of GER (heartburn, regurgitation of acid into the mouth, retrosternal pain, or dysphagia). The patients had received bronchodilator therapy: sustained-release theophylline, 200 mg qd or bid (n = 7), and beclomethasone dipropionate, 400 μg bid (n = 4). None of the patients received oral corticosteroids, and all refrained from medication for 24 h before the study. Caffeine-containing drinks were not allowed for 12 h before capsaicin challenge cough test, and β 2 -inhalants were withdrawn at least 8 h prior to testing. In addition, none of the patients tested in this study took any antacids, histamine type 2 blockers, or proton pump inhibitors for at least 14 days prior to the study.

In the present study, four asthmatics received HCl perfusion firstly and three asthmatics did secondly. There was no significant difference between the data at the first and second measurements including the HCl and saline perfusion. This result indicated that the increased cough sensitivity could be detected without an effect of the measuring order.

Log PD 3 revealed lower value during distal esophag-
ageal HCl perfusion (0.45 ± 0.04 nmol) compared with that of saline solution perfusion (0.04 ± 0.06 nmol) [p < 0.01; Fig 1]. However, no significant difference in FEV₁ was observed during distal esophageal saline solution perfusion and during HCl perfusion (saline solution, 1.96 ± 0.25 L vs HCl, 1.95 ± 0.24 L; n = 7; p = 0.88) [Fig 2, Table 2]. Neither FVC nor PEF components changed during distal esophageal HCl perfusions (FVC: saline solution, 2.51 ± 0.31 L, vs HCl, 2.50 ± 0.27 L; n = 7; p = 0.81; and PEF: saline solution, 5.79 ± 0.69 L/s, vs HCl, 5.64 ± 0.72 L/s; n = 7; p = 0.21) [Table 2].

**DISCUSSION**

While it has thus far remained unclear whether esophageal acid infusion itself can increase cough responsiveness in adults with bronchial asthma, results in the present study showed that cough responsiveness significantly increased after acid perfusion in the distal esophagus in patients with mild persistent bronchial asthma. To our knowledge, there has been no study to investigate the change of cough responsiveness during distal esophageal acid instillation with monitoring pH of the esophagus. We therefore monitored the pH of both the upper and lower part of the esophagus simultaneously, and report that no pH change was observed in the upper part of the esophagus during acid perfusion. These results convinced us that the pharynx had not been stimulated by the acid perfusion. In the present study, we demonstrated that distal esophageal acid perfusion itself can increase cough responsiveness in

![Figure 1. Changes in cough responsiveness (PD₃) to inhaled capsaicin during distal esophageal saline solution or HCl perfusion in patients with bronchial asthma. Log PD₃ decreased significantly during esophageal HCl perfusions (p < 0.01).](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21981/ on 06/27/2017)

![Figure 2. FEV₁ of individual patients during esophageal saline solution or HCl perfusion. FEV₁ during saline solution and during HCl perfusion were 1.96 ± 0.25 L and 1.95 ± 0.24 L, respectively. There was no significant change between the two values.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21981/ on 06/27/2017)

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**Table 1**—**Characteristics of Seven Study Patients With Bronchial Asthma**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Sex</th>
<th>GER Symptoms or Esophagitis</th>
<th>Asthma Duration, yr</th>
<th>Type of Asthma</th>
<th>Asthma Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>Female</td>
<td>None</td>
<td>8</td>
<td>Mild persistent</td>
<td>T</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>Female</td>
<td>None</td>
<td>7</td>
<td>Mild persistent</td>
<td>T, S</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>Female</td>
<td>None</td>
<td>5</td>
<td>Mild persistent</td>
<td>T</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>Male</td>
<td>None</td>
<td>18</td>
<td>Mild persistent</td>
<td>T, S</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>Male</td>
<td>None</td>
<td>6</td>
<td>Mild persistent</td>
<td>T</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>Female</td>
<td>None</td>
<td>4</td>
<td>Mild persistent</td>
<td>T</td>
</tr>
<tr>
<td>7</td>
<td>63</td>
<td>Male</td>
<td>None</td>
<td>5</td>
<td>Mild persistent</td>
<td>T, S</td>
</tr>
</tbody>
</table>

*T* = theophylline; and *S* = inhalation of steroid.
patients with mild persistent bronchial asthma even without GER symptoms and the presence of esophagitis. Twenty-four hour esophageal pH testing was very important in this study. Unfortunately, we could not agree on the subjects on which to perform the 24-h esophageal pH testing; therefore, we could not evaluate GER in the patients.

It was previously shown that chronic persistent cough that remains unexplained after a standard diagnostic evaluation is associated with either asymptomatic GER or impaired clearance of acid from the esophagus. Irwin et al indicated cough correlated with distal but not proximal acid reflux events, with endoscopy usually showing evidence of distal esophagitis. They concluded that acid stimulated inflamed distal esophageal mucosal receptors, resulting in a reflex-mediated cough. Ing et al suggested that acid in the distal esophagus precipitates cough, and that there is evidence for an esophageal-tracheobronchial cough reflex mechanism in patients with chronic cough associated with GER. However, their subjects were not asthmatic patients, and they did not study the change of cough responsiveness during esophageal HCl infusion. Furthermore, they did not perform esophagogastroscopy to reveal if their patients had esophagitis. In our study, we confirmed the patients with mild persistent bronchial asthma have neither GER symptoms nor esophagitis, which was evaluated by gastroesophagography.

Field indicated that asthmatics without symptomatic GER did not show any changes in FVC, FEV₁, and PEF during esophageal HCl perfusion. In the present study, we did not observe any significant changes of FVC, FEV₁, and PEF during esophageal HCl perfusion.

In the US National Asthma Education and Prevention Program guidelines, as a long-term control, sustained-release theophylline is listed in the treatment for the asthmatics with mild persistent asthma; however, it is not preferred as inhaled corticosteroid or cromolyn or nedocromil. In contrast, the Japanese Asthma Prevention and Management Guideline recommended sustained-release theophylline as the same as inhaled corticosteroid. In this regard, a higher ratio of asthmatics with mild persistent asthma are receiving theophylline in Japan compared to the patients in the United States.

Asthma is exacerbated by multiple triggers. One common, often overlooked trigger is GER. Sontag et al reported that 82% of 104 adult asthmatics had abnormal amounts of acid reflux, significantly lower LES pressure, more frequent reflux episodes, and higher esophageal acid contact times, evaluated by 24-h pH esophageal testing and esophageal manometry.

There are two proposed mechanisms of GER-associated cough: (1) acid in the distal esophagus stimulating an esophageal-tracheobronchial cough reflex, and (2) microaspiration or macroaspiration of esophageal contents into the larynx and tracheobronchial tree. We studied the GER-associated cough responsiveness while acid in the distal esophagus stimulated an esophageal-tracheobronchial cough reflex, though the mechanisms would need to be elucidated further. Hamamoto et al studied the airway plasma extravasation induced by intraesophageal HCl stimulation in anesthetized guinea pigs, and found that infusion of 1 N HCl into the esophagus significantly increased plasma extravasation in the trachea, which was inhibited by capsaicin or bilateral vagotomy. They thus concluded that tachykinin-like substances are released to cause plasma extravasation in the airways as a result of intraesophageal HCl stimulation, and there are neural pathways communicating between the esophagus and airways, including the vagus nerve. Capsaicin releases tachykinins from storage in nerve endings in the airway. Substance P is one of the potent tachykinins to stimulate C fiber and to induce cough. The increased capsaicin-induced cough sensitivity by HCl perfusion of lower esophagus was due to the increased susceptibility of C fiber-mediated vagal nerve network communicating between the airway and esophagus. In the present study, spontaneous coughing did not occur during the acid stimulation to esophagus on all subjects. Therefore, the acid stimulation to esophagus itself increased only cough sensitivity to capsaicin, but did not induce spontaneous cough. In this regard, GER may increase cough responsiveness when asthmatics receive stimuli to their airway.

In the present study, we observed patients with mild persistent asthma without GER symptoms or esophagitis. One may expect a further exaggerated

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>FVC Saline Solution</th>
<th>HCl</th>
<th>FEV₁ Saline Solution</th>
<th>HCl</th>
<th>PEF Saline Solution</th>
<th>HCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.28</td>
<td>1.30</td>
<td>1.04</td>
<td>1.02</td>
<td>3.36</td>
<td>3.27</td>
</tr>
<tr>
<td>2</td>
<td>2.12</td>
<td>2.16</td>
<td>1.60</td>
<td>1.64</td>
<td>6.13</td>
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<tr>
<td>3</td>
<td>2.96</td>
<td>2.95</td>
<td>2.76</td>
<td>2.70</td>
<td>5.88</td>
<td>5.97</td>
</tr>
<tr>
<td>4</td>
<td>3.33</td>
<td>3.31</td>
<td>1.68</td>
<td>1.64</td>
<td>4.15</td>
<td>4.04</td>
</tr>
<tr>
<td>5</td>
<td>3.90</td>
<td>3.96</td>
<td>2.86</td>
<td>2.85</td>
<td>8.71</td>
<td>8.59</td>
</tr>
<tr>
<td>6</td>
<td>3.22</td>
<td>3.21</td>
<td>1.96</td>
<td>1.94</td>
<td>5.04</td>
<td>4.73</td>
</tr>
<tr>
<td>7</td>
<td>2.65</td>
<td>2.68</td>
<td>1.80</td>
<td>1.85</td>
<td>7.23</td>
<td>6.74</td>
</tr>
<tr>
<td>Mean</td>
<td>2.51</td>
<td>2.50</td>
<td>1.96</td>
<td>1.95</td>
<td>5.79</td>
<td>5.64</td>
</tr>
<tr>
<td>SD</td>
<td>0.31</td>
<td>0.27</td>
<td>0.25</td>
<td>0.24</td>
<td>0.69</td>
<td>0.72</td>
</tr>
</tbody>
</table>
increase in cough responsiveness in patients with esophagitis or in patients with severe persistent asthma. However, it is still uncertain whether either case is true. In the present study, we did not examine nonasthmatic subjects. There is no report concerning the effect of HCl perfusion on cough sensitivity of normal subjects. However, Schmidt et al reported that in normal subjects and patients with mild bronchial asthma, cough thresholds were not significantly different from each other.

The present data suggest that artificially induced GER leads to an increase in cough responsiveness in patients with mild persistent asthma. The increased cough sensitivity itself does not cause an asthma attack. However, increased cough itself lowers the quality of life in asthmatics because of sleep disturbance, interruption of speech, etc. Our previous study also indicated that an increase in airway hyperresponsiveness was induced when HCl stimulated the esophagus in patients with bronchial asthma.

We conclude that acid stimulation of the lower esophagus increased cough responsiveness to capsaicin in patients with mild persistent asthma, even in those without GER symptoms or evidence of esophagitis. The clinical importance of this finding will require further investigation.

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REFERENCES
1 Ayres JG, Miles JF. Oesophageal reflux and asthma. Eur Respir J 1996; 9:1073–1078
2 Harding SM, Richter JE. The role of gastroesophageal reflux in chronic cough and asthma. Chest 1997; 111:1389–1402
4 Mays EE. Intrinsic asthma in adults: association with gastro-esophageal reflux. JAMA 1976; 236:2626–2628
11 Nishino T, Kochi T, Ishii M. Differences in respiratory reflex responses from the larynx, trachea, and bronchi in anesthetized female subjects. Anesthesiology 1996; 84:70–74
12 Wetmore RF. Effects of acid on the larynx of the maturing rabbit and their possible significance to the sudden infant death syndrome. Laryngoscope 1993; 103:1242–1254
20 Field SK. A critical review of the studies of the effects of simulated or real gastroesophageal reflux on pulmonary function in asthmatic adults. Chest 1999; 115:848–856